Adipose Depots, Not Disease-related Factors, Account for Skeletal Muscle Insulin Sensitivity in Established and Treated Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** In prior reports, individuals with rheumatoid arthritis (RA) exhibited increased insulin resistance. However, those studies were limited by either suboptimal assessment methods for insulin sensitivity or a failure to account for important determinants such as adiposity and lack of physical activity. Our objectives were to carefully assess, compare, and determine predictors of skeletal muscle insulin sensitivity in RA, accounting for adiposity and physical activity.

Methods. Thirty-nine individuals with established (seropositive or erosions) and treated RA and 39 controls matched for age, sex, race, body mass index, and physical activity underwent a frequently sampled intravenous glucose tolerance test to determine insulin sensitivity. Inflammation, body composition, and physical activity were assessed with systemic cytokine measurements, computed tomography scans, and accelerometry, respectively. Exclusions were diabetes, cardiovascular disease, medication changes within 3 months, and prednisone use over 5 mg/day. This investigation was powered to detect a clinically significant, moderate effect size for insulin sensitivity difference.

Results. Despite elevated systemic inflammation [interleukin (IL)-6, IL-18, tumor necrosis factor-α; $p < 0.05$ for all], persons with RA were not less insulin sensitive [S_I geometric mean (SD): RA 4.0 (2.4) vs control 4.9 (2.1)*10^{-5} min^{-1}/(pmol/l); $p = 0.39$]. Except for visceral adiposity being slightly greater in controls ($p = 0.03$), there were no differences in body composition or physical activity. Lower insulin sensitivity was independently associated with increased abdominal and thigh adiposity, but not with cytokines, disease activity, duration, disability, or disease-modifying medication use.

Conclusion. In established and treated RA, traditional risk factors, specifically excess adiposity, play more of a role in predicting skeletal muscle insulin sensitivity than do systemic inflammation or other disease-related factors. (J Rheumatol First Release July 1 2014; doi:10.3899/jrheum.140224)

Key Indexing Terms:
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In persons with rheumatoid arthritis (RA), 2-fold increased rates of cardiovascular (CV) disease have been attributed, in part, to insulin resistance[1,2]. Potential explanations for insulin resistance in RA have included higher systemic inflammation associated with active disease, use of glucocorticoids, and increased traditional risks such as abdominal obesity and inactivity[2,3].

Most prior investigations of insulin resistance in RA

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have relied largely on fasting measures that better reflect hepatic rather than skeletal muscle insulin sensitivity. Assessing insulin sensitivity is critical, because skeletal muscle is responsible for as much as 90% of glucose uptake after a meal. Further, skeletal muscle insulin resistance initiates and perpetuates the development of type 2 diabetes and serves as the central feature of the metabolic syndrome[4,5]. Of the few investigations in patients with RA that have used glucose challenge-based measures of insulin sensitivity, none have accounted for potential differences in adiposity and physical activity[6,7,8,9,10]. To improve understanding of how insulin resistance might contribute to increased CV risk in persons with RA, our objectives were to determine (1) whether persons with RA, as compared to controls matched for age, sex, race, body mass index (BMI), and physical activity, exhibit more skeletal muscle insulin resistance as assessed by intravenous (IV) glucose tolerance tests (IVGTT), and (2) in persons with RA, whether disease-specific and/or traditional predictors are related to skeletal muscle insulin resistance.

MATERIALS AND METHODS

Patient population. In this cross-sectional investigation, persons were included if they had (1) RA that met American College of Rheumatology 1987 criteria[11], (2) seropositive disease (positive rheumatoid factor or anticyclic citrullinated peptide) or evidence of erosions, and (3) no medication changes within the 3 months prior to study enrollment. Persons using prednisone 5 mg or less daily were included. Any prednisone taper must have been completed at least 3 weeks prior to enrollment. Healthy individuals without a diagnosis of RA or joint pain or swelling lasting more than a week were matched to an RA participant by sex, race, age (within 3 yrs), and BMI (within 3 kg/m^2). For 1 African American participant where a race match was not identified, a white person who was otherwise well-matched was included. Exclusion criteria were a history of diabetes or CV disease, current pregnancy, and use of medications known to affect carbohydrate or lipid metabolism (including insulin, oral antidiabetic agents, statins, fibrates, nicotinic acid, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or β blockers). Participants with RA were recruited from Duke University and Durham Veterans Affairs Medical Center Rheumatology Clinics and from the local community with newspaper and website advertisements. Controls were recruited from the local community with newspaper and Website advertisements. Our study was in compliance with the Helsinki Declaration and was approved by the Duke University Institutional Review Board. All participants gave written informed consent.

Questionnaires and physical examination. Participants completed questionnaires for medications, disability (Health Assessment Questionnaire Disability Index)[12], comorbidities[13], a visual analog scale for health rating, and the Stanford Brief Activity Survey for physical activity[14]. Each completed a visual analog scale (VAS) for health, and underwent anthropometric measures, a 28-joint examination, and fasting blood collection for glucose, insulin, and erythrocyte sedimentation rate (ESR). The VAS, joint examination, and ESR were used to compute a Disease Activity Score (DAS28)[15].

Accelerometry. Participants wore an RT3 tri-axial accelerometer (Stayhealthy Inc.) for 7 days. Data were obtained from accelerometers as activity calories per min (Stayhealthy RT3 Assist Version 1.0.6). Ninety consecutive min of no measured activity was used to indicate and eliminate periods of time when individuals were not wearing the device. Also, if there were fewer than 10 h of measured activity in a single day, all data from that day were excluded from analysis. Similarly, we excluded data from participants (n = 7) who had fewer than 4 days of valid data (each of 10 h or more of wear time). Two participants did not return the device.

Systemic inflammatory measures. A panel of proinflammatory cytokines including interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α were measured in plasma samples using a multiarray quantitative immunoassay (Meso Scale Discovery). IL-18 and high-sensitivity C-reactive protein (hsCRP) were measured using sandwich ELISA (R&D, and MP Biomedicals, respectively). Mean intraassay (within plate) coefficients of variation were as follows: IL-1β 9.3%, IL-6 3.4%, IL-8 3.9%, TNF-α 2.9%, IL-18 2.4%, and hsCRP 3.5%. A human plasma control was run on each plate, and mean interassay (between plates) coefficients of variation were as follows: IL-1β 5.5%, IL-6 3.0%, IL-8 7.8%, TNF-α 7.7%, IL-18 6.0%, and hsCRP 3.9%.

Insulin sensitivity and fatty acids. Insulin sensitivity was determined using a frequently sampled IVGTT. Glucose (50%) was injected through a catheter at 0.3 g/kg body mass. Insulin was injected at min 20 at 0.025 units/kg body mass. Twenty-nine blood samples were obtained over 3 hours, centrifuged, and stored at -80°C. Glucose was measured on a Beckman-CoulterDxC600 analyzer, and insulin by electrochemiluminescent assay from Meso Scale Discovery. Insulin sensitivity index was calculated using Bergman's minimal model[16]. Nonesterified free fatty acids (NEFA) were measured by colorimetric enzymatic assay using a Beckman-Coulter DxC600 analyzer, with reagents from Wako.

Abdomen and thigh computerized tomography (CT) scans. Single 10-mm-thick axial sections at the liver and mid-thigh were performed using a General Electric CT/I scanner (GE Medical Systems). Cross-sectional areas for adipose tissue depots and liver and muscle density were measured using OsiriX (Pixmeo). CT scan determinations of adipose tissue depots are very accurate, precise, and reliable[17,18].

Statistical analyses. Cytokines, NEFA, and insulin sensitivity index were logarithmically transformed prior to group comparisons. Comparisons between patients with RA and controls were performed with mixed models, which accounted for the repeated measure of matched participants. Bivariate associations were assessed with Spearman correlations. Multivariable modeling for insulin sensitivity index (log) was performed using linear models with backward stepwise variable selection. Initial variable inclusion was based on conceptual hypotheses regarding traditional risk factors and disease-associated factors affecting insulin sensitivity index and included age, sex, waist circumference, physical activity, disease activity (DAS28), disease-modifying agent use, biologic agent use, and prednisone use. Waist circumference was selected rather than BMI based on the high levels of correlation between the 2 (r = 0.87) and because waist circumference was more strongly correlated with insulin sensitivity index. For the laboratory model (based on results from bivariate analyses), visceral adiposity and thigh intermuscular adiposity were included rather than waist circumference, and IL-6 was included rather than disease activity; all other variables from the clinical model were included.

Statistical power. Our investigation was designed to detect a difference in insulin sensitivity that corresponded to a moderate effect size (0.4–0.5)[19]. Based on 39 matched pairs and an α of 0.05, we had 80% power to detect a standardized difference in insulin sensitivity index of 0.46.

RESULTS

Patients with RA were well matched to controls in age, sex, and BMI (Table 1). While patients with RA had slightly less abdominal visceral adiposity (p = 0.03), otherwise there were similar amounts of fasting NEFA, abdominal and thigh adipose tissue depots, and thigh muscle area and density (p > 0.05 for all). There were no differences in physical activity, measured as total energy expended (p > 0.05). In the context of a wide range of disease activity (DAS28

Table 1. Participant characteristics. Data are presented as means (SD) for continuous variables and number (%) of participants for dichotomous variables. Data that were not normally distributed (systemic inflammatory markers, cytokines, and insulin sensitivity) are presented as geometric means (SD).

Variable	All Participants, n = 78	Rheumatoid Arthritis, n = 39	Matched Controls, n = 39
Age, yrs	55.5 (11.8)	56.1 (12.4)	54.9 (11.4)
BMI, kg/m^2	30.2 (6.3)	30.5 (7.3)	30.0 (5.3)
Waist circumference, cm	94.9 (15.5)	95.1 (17.7)	94.6 (13.7)
Race			
White	59 (76)	29 (74)	30 (76)
African American	19 (24)	10 (26)	9 (24)
Sex			
Female	54 (69)	27 (69)	27 (69)
Male	24 (32)	12 (31)	12 (31)
Physical activity, kCal/day	572.8 (290.8)	546.6 (291.4)	605.1 (292.7)
Physical activity, METS h/day	29.5 (2.5)	29.2 (2.5)	29.9 (2.4)
Disease duration, mos	NA	159 (135)	NA
HAQ–Disability Index	0.5 (0.7)	0.7 (0.7)†	0.00 (0.00)
Comorbidity Index	1.2 (1.2)	1.5 (1.2) †	0.6 (0.9)
DAS28 mean (SD)	NA	3.1 (1.5)	NA
Remission (DAS28 < 2.6)		16 (42)	
Low activity (DAS28 2.6–3.2)		6 (16)	
Moderate activity (DAS28 3.2–5.1)		11 (29)	
High activity (DAS28 > 5.1)		5 (13)	
Rheumatoid factor–positive	NA	30/35 (86)	NA
Anticyclic citrullinated antibody-positive	NA	14/15 (93)	NA
Erosions on radiographs present	NA	18/30 (60)	NA
Medication use	NA		
Etanercept		8 (21)	NA
Infliximab		2 (5)	NA
Adalimumab		4 (10)	NA
Abatacept		5 (13)	NA
Methotrexate		29 (74)	NA
Leflunomide		1 (3)	NA
Sulfasalazine		0	NA
Hydroxychloroquine		6 (13)	NA
Nonsteroidal antiinflammatory agents		16 (41)	1 (5.5)
Prednisone (< 0.5 mg/day)		11 (28)	NA
Systemic inflammation			
hsCRP, mg/l	3.14 (4.1)	4.1 (5.5)	2.4 (2.9)
IL-1β, pg/ml	0.22 (5.4)	0.32 (4.2)	0.15 (6.3)
IL-6, pg/ml	5.3 (2.8)	9.9 (2.9)†	2.9 (1.6)
IL-8, pg/ml	8.5 (2.1)	9.4 (1.9)	7.7 (2.4)
TNF-α, pg/ml	14.1 (2.3)	21.6 (2.4)†	9.4 (1.6)
IL-18, pg/ml	413.0 (1.3)	446.7 (1.2)†	316.2 (1.4)
Insulin Sensitivity Index 10^{-5} min^{-1}/pmol/l			
All	4.5 (2.2)	4.0 (2.4)	4.9 (2.1)
Women	5.0 (2.3)	4.7 (2.4)	5.2 (2.2)
Men	3.6 (2.1)	3.1 (2.3)	4.0 (1.9)
Biologic use = yes	NA	4.8 (2.4)	NA
Biologic use = no	NA	3.7(2.4)	NA
DMARD use = yes	NA	4.0 (2.5)	NA
DMARD use = no	NA	5.4 (1.7)	NA
Prednisone use = yes	NA	3.2 (2.1)	NA
Prednisone use = no	NA	4.8 (2.4)	NA
NEFA (mmol/l)	0.55 (1.47)	0.57 (1.57)	0.53 (1.36)
Adiposity and muscle tissue			
Abdominal total adipose area, cm^2	430 (179)	407 (199)	453 (157)
Abdominal subcutaneous adiposity, cm^2	306 (144)	302 (149)	309 (141)
Abdominal visceral adiposity, cm^2	125 (98)	105 (81)†	144 (109)
Abdominal liver density, Hu	60 (10)	60 (9)	60 (10)
Thigh total area, cm^2	254 (65)	253 (69)	255 (61)
Thigh total adipose area, cm^2	127 (66)	137 (61)	116 (70)
Thigh subcutaneous adiposity, cm^2	121 (57)	125 (58)	117 (57)
Thigh intermuscular adiposity, cm^2	11 (8)	12 (7)	11 (8)
Thigh muscle area, cm^2	120 (36)	116 (39)	125 (33)
Thigh muscle density, Hu	51 (5)	50 (6)	52 (4)

†$p < 0.05$ for comparison with matched controls. BMI: body mass index; NA: not applicable; HAQ: Health Assessment Questionnaire; DAS28: 28-joint Disease Activity Score; hsCRP: high-sensitivity C-reactive protein; IL: interleukin; METS: metabolic equivalence units; TNF: tumor necrosis factor; DMARD: disease-modifying antirheumatic drugs; NEFA: nonesterified free fatty acids.

0.78–6.4) and duration (5–506 mos), individuals with RA exhibited a proinflammatory profile, as demonstrated by elevated TNF-α, IL-6, and IL-18 ($p < 0.05$ for all). Despite elevated systemic inflammation, persons with RA were not significantly less insulin-sensitive than controls [insulin sensitivity index (S_I) geometric mean (SD) = 4.0 (2.4) vs 4.9 (2.0)*10^{-5} min^{-1}/(pmol/l); mean SD for log $S_I = 0.23$; $p = 0.39$].

Table 2 shows correlations of key traditional and disease-specific risks with insulin sensitivity. In persons with RA, lower insulin sensitivity index was associated with a larger BMI ($r = –0.45$, $p < 0.002$), a greater waist circumference ($r = –0.47$, $p < 0.001$), and increased amounts of total abdominal adipose tissue, visceral adiposity, total thigh area, thigh intermuscular adiposity, and thigh muscle area ($r = –0.3$ to 0.5, $p < 0.05$ for all).

Multivariable modeling was performed using variables available in a clinic setting: age, sex, waist circumference, physical activity, disease activity, biologic use, use of disease-modifying antirheumatic drugs, and prednisone use.

Table 2. Spearman correlations for insulin sensitivity, n = 44.

Variable	Spearman ρ (R)	p
Age, yrs	–0.16	0.29
BMI, kg/m^2	**–0.45**	**0.002**
Waist circumference, cm	**–0.47**	**0.001**
Sex (male = 0, female = 1)	0.20	0.20
Physical activity, kCal/day	–0.08	0.66
Physical activity, METS h/day	0.19	0.27
Disease duration	0.16	0.32
HAQ Disability Index	–0.21	0.17
DAS28	–0.12	0.44
Biologic use, yes = 1, no = 0	0.14	0.37
DMARD use, yes = 1, no = 0	–0.16	0.29
Prednisone use, yes = 1, no = 0	–0.28	0.07
hsCRP, mg/l	–0.18	0.25
IL-1β, pg/ml	0.04	0.82
IL-6, pg/ml	**–0.30**	**0.05**
IL-8, pg/ml	–0.09	0.56
TNF-α, pg/ml	–0.08	0.62
IL-18 (pg/ml)	–0.20	0.20
NEFA	–0.28	0.06
Abdominal total adipose area, cm^2	**–0.43**	**0.005**
Abdominal subcutaneous adiposity, cm^2	–0.30	0.06
Abdominal visceral adiposity, cm^2	**–0.48**	**0.002**
Abdominal liver density, Hu	0.27	0.10
Thigh total area, cm^2	**–0.38**	**0.01**
Thigh total adipose area, cm^2	–0.20	0.20
Thigh subcutaneous adiposity, cm^2	–0.15	0.32
Thigh intermuscular adiposity, cm^2	**–0.52**	**0.0004**
Thigh muscle area, cm^2	**–0.36**	**0.02**
Thigh muscle density, Hu	0.12	0.45

Data given in bold face are statistically significant. BMI: body mass index; HAQ: Health Assessment Questionnaire; DAS28: 28-joint Disease Activity Score; DMARD: nonbiologic disease-modifying antirheumatic drug; hsCRP: high-sensitivity C-reactive protein; METS: metabolic equivalence units; IL: interleukin; TNF: tumor necrosis factor; NEFA: nonesterified free fatty acids.

After backward variable selection, the model retained only waist circumference and accounted for 26% of the variance in insulin sensitivity index (Table 3, $p < 0.0005$). To better understand the contribution of inflammation and adiposity, a "laboratory" model was constructed. For this model, initial variables included visceral adiposity and thigh intermuscular adiposity rather than waist circumference, IL-6 rather than disease activity, and all of the other variables in the initial clinical model. In the laboratory model, visceral adiposity, thigh intermuscular adiposity, and IL-6 accounted for 46% of the variance in insulin sensitivity index (Table 3; $p < 0.0005$). Visceral adiposity ($p < 0.005$) and thigh intermuscular adiposity ($p < 0.02$) were each independently related to insulin sensitivity index.

DISCUSSION

In 39 persons with established RA (well controlled and reflective of many clinic cohorts), insulin sensitivity index, as measured with an IVGTT, was not significantly lower than in matched controls. Also, for persons with RA, insulin sensitivity was related to traditional risk factors of large adipose tissue depots. Other than concentrations of IL-6, disease-specific factors, including disease activity, biologic agent use, and disease-modifying agent use had little apparent influence on this outcome.

To our knowledge, this is the first well-controlled comparison of insulin sensitivity index for persons with established and treated RA. Previously, most studies addressing insulin sensitivity in RA used fasting glucose-derived and insulin-derived indices such as homeostasis model assessment and the quantitative insulin sensitivity check index[2]; however, those fasting-derived indices reflect insulin sensitivity mainly in the liver. In contrast,

Table 3. Multivariable model for insulin sensitivity index (log) in persons with rheumatoid arthritis.

	Variable Estimate	Partial R^2	p
Clinical model: $R^2 = 0.26$			
Waist circumference, cm	–0.01	0.26	0.0005
Laboratory model: $R^2 = 0.46$			
Visceral adiposity area, cm^2	–0.002	0.28	0.005
Thigh intermuscular adiposity area, cm^2	–0.02	0.12	0.02
IL-6, log pg/ml	–0.22	0.07	0.07

Multivariable modeling was performed using linear models with backward stepwise variable selection. For the clinical model, variable inclusion was based on conceptual hypotheses regarding traditional risk factors and disease-associated factors affecting insulin sensitivity index and included age, sex, waist circumference, physical activity, disease activity (28 joints), disease-modifying agent use, biologic use, and prednisone use. Based on results from bivariate analyses, for the laboratory model, waist circumference was replaced with visceral adiposity and thigh intermuscular adiposity, and disease activity was replaced with interleukin (IL)-6; all other variables from the clinical model were included.

glucose tolerance tests better reflect insulin sensitivity in skeletal muscle. Because skeletal muscle is responsible for the majority (up to 90%) of systemic glucose uptake after a glucose load such as during a meal, assessing insulin sensitivity index with glucose challenge tests is critical for understanding insulin action.

Despite the importance outlined above, glucose challenge tests, including oral and IV glucose loads as well as euglycemic clamps, have been used to compare insulin sensitivity between RA and controls in a relatively small number of investigations[6,7,8,9,10,20]. Findings from these have been conflicting, likely because of a failure to adequately assess and account for the significant contributors to insulin resistance, adiposity, and physical inactivity. Specifically, several investigations demonstrated that persons with untreated RA had greater insulin resistance, but none included BMI-matched controls or assessed physical activity[8,9,20]. Also, in 2 investigations, persons with RA had insulin sensitivity similar to that of controls, but in one, the comparison was confounded by the control group having more males and higher BMI[6]. The second investigation was limited to normal weight, premenopausal females, limiting generalizability. Our study shows definitively that despite elevated amounts of systemic inflammation when compared to controls matched for adiposity and physical inactivity, persons with RA have similar insulin sensitivity.

Thus, in typical clinical cohorts of established and well-controlled RA, the average reduction in insulin sensitivity index imposed by RA-associated factors appears both statistically and clinically insignificant. Statistical power for this investigation aimed to detect a difference in insulin sensitivity corresponding to a moderate effect size, so the observed small difference was not statistically significant. Clearly, a larger sample might have been able to detect the small difference as statistically significant, but the critical issue is the clinical relevance of such a small difference in insulin sensitivity.

Clinical relevance for specific insulin sensitivity values is difficult to determine, but some investigations linking insulin sensitivities to outcomes can provide insight into this issue. When persons were followed longitudinally for 25 years for diabetes development, the difference was much larger than ours between those who developed type 2 diabetes and those who did not [3.2 ± 2.4 vs 8.1 ± 6.7 10^{-5} min^{-1}/(pmol/l)][21]. Also, when comparing tertiles of insulin sensitivity, the upper tertile ($\geq 2.39*10^{-5}$ min^{-1} /[pmol/l]) was associated with an incidence of progression of $< 10\%$[22]. This low incidence suggests that the effect of the small difference observed between persons with well-controlled RA and matched controls is clinically negligible.

As a means of confirming that risk of insulin sensitivity in well-controlled RA is similar to that of matched controls, we observed that predictors of insulin sensitivity in RA are largely traditional cardiometabolic risk factors rather than RA-specific ones. Prior predictors of RA-associated insulin resistance include both altered body composition and inflammation[2,3,6,9]. Covering a wide range of insulin sensitivities and disease activities, our sample provided a rich source to identify potential unique mediators of insulin resistance development in persons with RA. Nonetheless, except for IL-6 concentrations, all correlates of insulin sensitivity were to body composition. These findings imply that in persons with established and treated RA, traditional risk factors, specifically excess adiposity, play more of a role in predicting insulin sensitivity index than do inflammation or medication use.

A wide range of hypotheses and evidence link adipose tissue and skeletal muscle insulin resistance. Adipose tissue contributes to skeletal muscle insulin resistance by providing a source of free fatty acids, which inhibit insulin-stimulated glucose uptake in skeletal muscle both directly and indirectly (by promoting production of acyl-CoA and reactive oxygen species)[23]. Additionally, adipose tissue triggers skeletal muscle insulin resistance through the production of a number of insulin resistance-promoting inflammatory cytokines and adipokines[24].

While adipose tissue clearly contributed, skeletal muscle insulin resistance in RA appeared to have little relation to disease-specific factors. Of these, only IL-6 was related. Specifically, higher IL-6 was related to poorer insulin sensitivity, with a p value of 0.05 in bivariate analyses and a trend toward statistical significance in a multivariable model. In persons without systemic inflammatory disease, IL-6 has shown a complex relationship with insulin sensitivity[25]. Acutely, increases in IL-6 associated with exercise have been shown to improve insulin sensitivity, but chronic elevations appear to worsen insulin sensitivity[25]. Here, in persons with elevated systemic concentrations of IL-6, this cytokine was related to poorer insulin sensitivity in contrast to other disease-related variables.

We are aware that this investigation has limitations. One of the main limitations is a small sample size, in turn reducing study power and increasing the likelihood of a Type II statistical error. That, and the heterogeneity of our population, may have contributed to our lack of statistical significance in the difference in insulin sensitivity between RA and matched controls. However, heterogeneity provided a valuable opportunity to determine predictors of insulin sensitivity in persons with RA. Nonetheless, we recognize that the predictive capability of the models presented is relatively modest. However, developing models as tools for predicting insulin sensitivity was not the study goal, but rather the objective was to determine the relative contribution of disease-related and traditional risk factors for insulin resistance in RA. Also, we believe this sample of persons with established and treated RA reflects what is seen in many rheumatology clinic cohorts, thus allowing generalizability of our findings regarding risks for insulin

sensitivity in RA. One of the main strengths is using IVGTT to assess insulin sensitivity index in RA, thus emphasizing that stimulated tolerance tests allow a more complete assessment of insulin action.

Thus, in a population of patients with RA reflective of typical clinical cohorts, as compared to well-matched controls, insulin sensitivity index was not significantly lower in those with RA. Increased abdominal and thigh adiposity contributed to poorer insulin sensitivity but not disease activity or medication use. These findings imply that in established and treated RA, adipose depots, not disease-related factors, account for insulin sensitivity.

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REFERENCES

1. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum 2005;52:402-11.
2. Dessein PH, Joffe BI, Stanwix AE. Editorial: should we evaluate insulin sensitivity in rheumatoid arthritis? Semin Arthritis Rheum 2005;35:5-7.
3. Chung CP, Oeser A, Solus JF, Gebretsadik T, Shintani A, Avalos I, et al. Inflammation-associated insulin resistance: differential effects in rheumatoid arthritis and systemic lupus erythematosus define potential mechanisms. Arthritis Rheum 2008;58:2105-12.
4. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care 2009;32 Suppl 2:S157-63.
5. Petersen KF, Dufour S, Savage DB, Bilz S, Solomon G, Yonemitsu S, et al. The role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome. Proc Natl Acad Sci U S A 2007;104:12587-94.
6. Hoes JN, van der Goes MC, van Raalte DH, van der Zijl NJ, den Uyl D, Lems WF, et al. Glucose tolerance, insulin sensitivity and beta-cell function in patients with rheumatoid arthritis treated with or without low-to-medium dose glucocorticoids. Ann Rheum Dis 2011;70:1887-94.
7. Penesova A, Radikova Z, Vlcek M, Kerlik J, Lukac J, Rovensky J, et al. Chronic inflammation and low-dose glucocorticoid effects on glucose metabolism in premenopausal females with rheumatoid arthritis free of conventional metabolic risk factors. Physiol Res 2013;62:75-83.
8. Svenson KL, Pollare T, Lithell H, Hallgren R. Impaired glucose handling in active rheumatoid arthritis: relationship to peripheral insulin resistance. Metabolism 1988;37:125-30.
9. Hallgren R, Berne C. Glucose intolerance in patients with chronic inflammatory diseases is normalized by glucocorticoids. Acta Med Scand 1983;213:351-5.
10. Rosenvinge A, Krogh-Madsen R, Baslund B, Pedersen BK. Insulin resistance in patients with rheumatoid arthritis: effect of anti-TNFalpha therapy. Scand J Rheumatol 2007;36:91-6.
11. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
12. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. J Rheumatol 2003;30:167-78.
13. Rigler SK, Studenski S, Wallace D, Reker DM, Duncan PW. Co-morbidity adjustment for functional outcomes in community-dwelling older adults. Clin Rehabil 2002;16:420-8.
14. Taylor-Piliae RE, Haskell WL, Iribarren C, Norton LC, Mahbouba MH, Fair JM, et al. Clinical utility of the Stanford brief activity survey in men and women with early-onset coronary artery disease. J Cardiopulm Rehabil Prev 2007;27:227-32.
15. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
16. Bergman RN, Ider YZ, Bowden CR, Cobelli C. Quantitative estimation of insulin sensitivity. Am J Physiol 1979;236:E667-77.
17. Irving BA, Weltman JY, Brock DW, Davis CK, Gaesser GA, Weltman A. NIH ImageJ and Slice-O-Matic computed tomography imaging software to quantify soft tissue. Obesity 2007;15:370-6.
18. Ellis KJ. Human body composition: in vivo methods. Physiol Rev 2000;80:649-80.
19. Cohen J. Statistical power analysis for the behavioral sciences. Second ed. Hillsdale, NJ: Lawrence Erlbaum Associates Inc.; 1988.
20. Paolisso G, Valentini G, Giugliano D, Marrazzo G, Tirri R, Gallo M, et al. Evidence for peripheral impaired glucose handling in patients with connective tissue diseases. Metabolism 1991; 40:902-7.
21. Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR. Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study. Lancet 1992;340:925-9.
22. Lorenzo C, Wagenknecht LE, Rewers MJ, Karter AJ, Bergman RN, Hanley AJ, et al. Disposition index, glucose effectiveness, and conversion to type 2 diabetes: the Insulin Resistance Atherosclerosis Study (IRAS). Diabetes Care 2010;33:2098-103.
23. Muoio DM, Neufer PD. Lipid-induced mitochondrial stress and insulin action in muscle. Cell Metab 2012;15:595-605.
24. Romacho T, Elsen M, Rohrborn D, Eckel J. Adipose tissue and its role in organ crosstalk. Acta Physiol 2014;210:733-53.
25. El-Kadre LJ, Tinoco AC. Interleukin-6 and obesity: the crosstalk between intestine, pancreas and liver. Curr Opin Clin Nutr Metab Care 2013;16:564-8.